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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,816	03/27/2002	Michael Valentine Agrez	ADAM-046XX	9944

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1643	
MAIL DATE	**DELIVERY MODE**
08/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/019,816	AGREZ ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *217-219,221,225,238,244,266,267,269,272,275,277 and 278* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *217-219,221,225,238,244,266,267,269,272,275,277 and 278* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *May 24, 2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 25, 2007 has been entered.

Claims 217, 266, 272, 275, 277 and 278 have been amended. Claims 245, 268, 276 and 279-282 have been canceled. Claims 217-219, 221, 225, 238, 244, 266, 267, 269, 272, 275, 277 and 278 are pending and under consideration.

Acknowledgement is made of applicants re-submission of the foreign priority documents, AU 124899D and AU 800300D.

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(a-d and f) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. AU 124899D and Application No. AU 800300D, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The foreign priority documents fail to provide an adequate written description of a method of treating cancer comprising administering cytoplasmic domains of B3 and B5 , which domains are responsible for binding to MAP kinase. One of skill in the art would reasonable conclude that

applicant was not in possession of the instant claimed method until the disclosure of PCT/AU00/00729 (WO01/00677), filed June 28, 2000.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 277 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 277 is vague and indefinite because it depends in part on canceled claim 220.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 217-219, 221, 225, 238, 244, 266, 267, 269, 272, 275, 277 and 278 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re wands, 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988).
(A)As drawn to a method of treating cancer comprising providing a mammalian patient believed to be at risk of suffering from cancer

Claims 266, 267, 269 and 272 require carrying out the claimed method in patients believed to be a risk of suffering from cancer.

In order to carry out the claimed method for prevention, it would be necessary to know which individuals are at risk for developing cancer, the location of said cancer, the time at which the cancer would develop, and the length of time before said development of the cancer at which the instant methods should commence in order to be effective. The specification fails to address any of these issues, thus one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to ;practice the claimed methods on patients believed to be at risk from suffering from cancer.

Applicant argues that the examiner failed to note that the claims are no longer drawn to the prophylaxis of cancer. This is not persuasive. Claim 266 persist in requiring patients believed to be at risk of suffering from cancer.. The treatment of said group of patients would constitute prophylaxis.

(B)As drawn to the direct interaction between the JNK or ERK MAP kinase families and integrin beta subunits

The claims are broadly drawn to methods of treating cancer or inhibiting the growth of cancer, said methods relying on the binding of a cytoplasmic fragment of a integrin β3, β5 or β6 to any MAP kinase. It is noted that the wherein clause specifies that the modified polypeptide binds to ERK2 but does not require that the unmodified β3, β5 or β6 fragments bind to the ERK2 MAP kinase. The art recognizes that MAP kinases comprising three different families: the ERK, JNK and p38, and that individual members participate in different signaling cascades (Garington and Johnson, Current Opinion in Cell Biology, 1999, Vol. 11, pp. 211-218, reference of the IDS filed July 30, 2002, page 212, figure 1) and are regulated by different scaffolding proteins (ibid, page 213, figure 2). Because MAP kinases such as ERK3-5 and p38 are present in entirely different signaling cascades and are bound by different scaffolding proteins such as MP-1 which binds to ERK1 and JIP-1 or MEKK1 both of which lead to enhanced JNK activation, one of skill in the art would reasonably conclude that the binding of ERK1 or JNK directly to the cytoplasmic domain of beta6 did not provide a nexus for the binding of any MAP kinase directly to beta6 or any other integrin beta subunit because the MAP kinases differ in protein-protein interactions with other known members in signaling cascades as exemplified by figure 2 of

Garington and Johnson. Given the lack of objective evidence in the specification for the antagonism of signaling between MAP kinases which were not ERK2 or JNK-1 and integrin beta subunit which was beta6 or any other integrin as a method of treating cancer, one of skill in the art would be subject to undue experimentation in order to practice the broadly claimed method because it is unknown what importance the signaling between beta 3 or 6 and other MAP kinases have on the cancerous phenotype.

(C)As drawn to modified polypeptides .

Claims 217, 218, 219, 221, 225, 238, 245, 266-269, 272-282 are drawn to methods reliant on the identity of a modified amino acid sequence having at least 60% overall identity with the binding domain of β3, β5 or β6, wherein said modified polypeptide bind to ERK2. The specification teaches peptides which comprise the integrin-map kinase binding domain and the peptides of SEQ ID NO:2, 3, 22 and 23. The specification fails to teach any structural correlation between retaining or varying the integrin binding domain sequence and the effect on the binding to any ERK2. The art recognizes that the binding of two proteins is influenced by the three dimensional conformation of each of the proteins. Variation of the primary amino acid sequence can have unforeseen consequences on a three dimensional protein structure because the three dimensional structure is governed by numerous interacting forces (Ibragimova and Eade, Biophysical Journal, Oct 1999, Vol. 77, pp. 2191-2198, cited in a previous action, see page 2191, first column, lines 12-17 and second column, lines 3-8). It is concluded that the art is unreliable for predicting the outcome of amino acid alterations on the three dimensional structure of a protein, and therefore the activity of said protein. It is noted that in order to practice the instant invention to the full scope of the claims it would be necessary to make a modified amino acid sequence having 60% identity to β3, β5 or β6, wherein said amino acid sequence would function as claimed in a method of treating cancer. The specification provides no objective evidence that such a variant can be made an retain the ability to interrupt signaling from β3, β5 or β6.

Given the lack of teachings in the specification regarding methods reliant on MAP kinases beyond those or EKR2 and JNK, and the lack of teachings in the specification regarding the making of the required sufficiently homologous polypeptides, one of skill in the art would be subject to undue experimentation in order to practice the broadly claimed methods.

(D) As drawn to the administration of polypeptides in vivo

Claims 266, 267, 269 and 272 require the administration of the instant peptides to a patient having a naturally occurring tumor, including human patients. Claims 217-219, 221, 225, 238, 244, 275, 277 and 278 encompass the administration of the instant peptides to a patient having a naturally occurring tumor, including human patients. The specification demonstrates that fusion protein comprising SEQ ID NO:4 and penetratin inhibits the growth of cancer cell lines, such as SW480 cells expressing beta 6. The art recognizes general problems with the administration of protein drugs, namely short half-life in vivo, necessitating multiple administrations (Johnson and Tracey, 'Peptide and Protein Drug Delivery', In: Encyclopedia of Controlled Drug Delivery, Vol. 2, 1999, pages 816-833, cited in a previous action). The art teaches that "major stability, release and manufacturing challenges" (page 816, second column, lines 1-5) must be met in order to overcome the technical difficulties associated with the delivery of proteins in vivo. The specification does not teach a means for the delivery of the polypeptide agents to the appropriate site and the efficacious uptake by the tumor to result in the inhibition of cancer cells in a patient. Therefore it would be undue experimentation in order for one of skill in the art to determine the required dosage for the required length of time, and the means to stabilize and then release said polypeptides in vivo using techniques which preserve the ability of said polypeptides to function as claimed. Further, Mohanlal (WO 02/40717, page 1, lines 12-26) teaches that

an important reason for the high failure rate in clinical trials is the poor predictive value of currently used screening technologies for biological validation, pharmacological testing, and screening for success or failure of chemical entities and biologicals in clinical trials involving human subjects. These screening technologies are based on in vitro cell-based screening models and in vivo animal models, which often lack or inadequately represent the clinical disease phenotype of the patients in which the tested chemical entities or biologicals are intended to be used in the future. Therefore, success of these chemical entities or biologicals in these models does not necessarily translate into clinical success in patients. Hence, the majority of chemical entities or biologicals, while successful in these preceding screening and animal models, fail in clinical trials, particularly in late phase II and phase III trials(38). It has been estimated that more than 90% of new chemical entities(NCEs) fail in clinical trials, of which approximately two

third fail for pharmacodynamic reasons (lack of efficacy and/or an unacceptable adverse event profile); the remaining third fail for pharmacokinetic reasons (3).

In the instant case, data from a cell line such as SW480 expressing B6 inadequately represents the clinical disease of a patient and therefore success from an inhibition in a cell culture does not translate into clinical success in patients. It is noted that in a cell culture model there is no objective evidence at all for positive pharmacodynamics or pharmacokinetics as stated above.

Given the lack of objective evidence in the specification for a method of treating actual non-experimental patients having naturally occurring tumors, and the lack of guidance regarding how to overcoming the problems recognized by the art as set forth above, one of skill in the art would be subject to undue experimentation without a reasonable expectation of success in order to practice the claimed methods.

Applicant argues that the specification is enabling for the instant methods through the specific examples provided. This has been considered but not found persuasive. The examples provide only for the inhibition of B6 expressing cells in culture, which for the reasons set forth above, do not provide for a nexus of inhibiting naturally occurring cancer cells in a patient..

Claims 277 and 278 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 277 has been amended to recite, "wherein the polypeptide is greater than 5 amino acids and up to 20 amino acids in length. Claim 278 has been amended to recite that the polypeptide is 10 amino acids or 15 amino acids in length. the originally filed disclosure does not support either of the amended claims. Page 49, lines states that the length of the polypeptide will be from about 5 amino acids to about 25 amino acids, which fails to provide for the new range of "greater than 5 amino acids and up to 20 amino acids". With regard to claim 278, it is

noted that he specification discloses three 15-mers and one 10-mer which fails to adequately describe the genus of polypeptides of 10 amino acids in length or a genus of polypeptide s of 10-mer in length. One of skill in the art would reasonable conclude that applicant was not in possession of the genus of polypeptides on which the instant claim relay and therefore applicant was not in possession of the claimed methods.

All other rejections and objections as set fort or maintained in the previous Office action are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A. Canella/
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Art Unit 1643